RESEARCH HIGHLIGHT

Profiling spatial gene activity in marmoset embryos

Guangdun Peng[1] and Patrick P. L. Tam[2]✉

Cell Research (2022) 32:873–874; https://doi.org/10.1038/s41422-022-00703-0

Spatial transcriptomics of the marmoset embryo unveils insights into the molecular landscape of post-implantation development and provides a reference dataset of cell and tissue identity and the mechanistic attributes of germ layer formation. The knowledge gains of the developmental coordinates of early gastrulation point to the utility of this non-human primate for modeling post-implantation development of human embryos.

The wealth of knowledge of the developmental biology of the mouse has hallmarked the laboratory mouse as a model organism for mammalian development. Significant progress has been achieved, through the analysis of genome function in gene-perturbation experimentation and the profiling of omics attributes of cell populations in developing embryos, in delineating morphogenetic mechanism, cell lineage trajectory and molecular drivers underpinning the development of preimplantation and early post-implantation mouse embryo. Recent works on profiling transcriptional activity at spatiotemporal and cellular resolution have defined a compendium of developmental coordinates, in morphogenetic and molecular context, of mouse development from peri-implantation to encompassing gastrulation and early organogenesis.[1–3] Gastrulation is a key developmental milestone at which the germ layer tissues that are blocking blocks of the body parts and organs are laid down as a blueprint of embryonic development. Human embryo research has been constrained by ethics and legal consideration and compounded by accessibility of embryo samples and technical challenges in experimentation. There are, hence, gaps of knowledge of early human development, particularly around the stage of gastrulation. In light of the innate differences in the cellular and molecular mechanisms of early embryo development between mouse and human,[4] and the morphogenetic process leading to dissimilar geometry of the gastrula-stage embryos and the accompanying discordance of the spatiotemporal profile of inductive interaction that guides cell differentiation and tissue patterning, questions have been raised regarding whether the learnings of mouse development can be extrapolated to modeling the development of early human embryos. There is, therefore, a strong imperative to model human development in an evolutionally more proximal mammalian species. In this regard, the non-human primates, such as the rhesus macaque and the marmoset, which display morphogenetic events during embryogenesis that are overtly similar to human, are hailed as the best-fit models. As a small, nonendangered New World primate, marmoset is less expensive to maintain in a laboratory setting, and, compared to macaque, the post-implantation embryos are more accessible and amenable for low-throughput analytical approaches.

Previously, profiling the transcriptome of cell lineages in the marmoset embryos at pre- to peri-implantation has defined the pluripotency and lineage trajectories of the blastocyst cell types.[3,5] Now, Bergmann and colleagues have extended the transcriptome analysis to post-implantation embryos and performed a spatial profiling of transcriptome of embryos of Carnegie stages 5–7 up to the stage of gastrulation.[6] In this study, a laser capture microdissection (LCM)-based spatial transcriptome approach was undertaken to sample 1–3 cells each time from embryonic, extraembryonic, and uterine tissues. Albeit time-consuming and limited in throughput, LCM-based Smart-seq2 method has a high gene detection ability, with an average of 8000 genes per sample being profiled. This data capture capability facilitates the 3D reconstruction of the signaling landscape and transition of pluripotency states.

From this rich information of 3D and spatial gene expression, the study of the marmoset embryos reiterates an overall conserved set of genetic determinants for embryonic patterning and germ layer formation in mouse and human. For example, expression of primitive streak markers is regionalized in the posterior pole of the embryonic disc, and WNT signaling ligands are expressed in the posterior side driving gastrulation. However, the authors also identified primate-specific markers of anterior visceral endoderm (VE)-like cells in the hypoblast, such as SDC4, POSTN, and FZD5. Primate-specific second yolk sac (SYS) endoderm arises from edges of the early VE and expresses both early VE marker and later SYS markers. The marmoset dataset provides hints for the role of BMP signaling in amnion formation. Using marmoset stem cell-based embryo models, the authors verified that BMP and OCT4 (POU5F1) are essential for amnion formation. Like the macaque embryo,[7] the amniotic epithelium and the early amnion of the marmoset embryo express BMP agonists, which function as the source of BMP signal, instead of the extraembryonic ectoderm in the mouse embryo. The spatial molecular features revealed a substantial convergence of the molecular attributes of primate embryogenesis,[8,9] which sets the foundation of utilizing the marmoset embryo to model early development of primates including the human.

It is widely accepted that the pluripotency spans a continuum of distinct cell states during mouse embryogenesis.[10] In the marmoset, the localization of core pluripotency genes in the anterior region of the embryonic disc and the co-existence of pluripotent and gastrulating cells in the early post-implantation

[1]Center for Cell Lineage and Development, CAS Key Laboratory of Regenerative Biology, Guangdong Provincial Key Laboratory of Stem Cell and Regenerative Medicine, GIBH-HKU Guangdong-Hong Kong Stem Cell and Regenerative Medicine Research Centre, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Guangzhou, Guangdong, China. [2]Embryology Research Unit, Children's Medical Research Institute, and School of Medical Sciences, Faculty of Medicine and Health, University of Sydney, Sydney, NSW 2145, Australia. ✉email: ptam@cmri.org.au

Published online: 20 July 2022

embryos reinforced the notion that epiblast cells display spatial heterogeneity in pluripotency.[1] There are, however, noted differences in the expression of core pluripotency factors between marmoset and mouse, where in the latter Nanog and Oct 4 are more strongly expressed in the posterior epiblast. Parallel studies in the 2D-micropattern gastruloids and the 3D embryoid models revealed a concordance of the spatial heterogeneity of pluripotency states and the signaling landscape, pointing to the notion that the spatiotemporal modulation of signaling activity enables capturing the various pluripotent states in the course of lineage specification and differentiation.

Recently, research on human stem cell-based embryo models has thrown light on the cellular events and molecular drivers of embryogenesis and germ layer development. However, the fidelity of these models in recapitulating the developmental coordinates of the natural embryos in vivo is yet unresolved. The study of the marmoset stem cell-based 2D gastruloid and post-implantation embryoid models showed that, by referencing to the developmental coordinates gleaned from the spatial transcriptome, the embryo model could recapitulate the developmental attributes of germ layer specification and event of embryogenesis inferred from the spatial transcriptome. These findings point to the utility of the stem cell-based models to investigate early embryo development of primates, and more importantly, the knowledge of the developmental coordinates of this non-human primate may provide a relevant reference for the elucidation of early human development in health and diseases. Besides that, such knowledge would have implication in the application of stem cell biology and organoid biology in advancing stem cell therapies for regenerative medicine.

REFERENCES

1. Peng, G. et al. *Nature* **572**, 528–532 (2019).
2. Pijuan-Sala, B. et al. *Nature* **566**, 490–495 (2019).
3. Boroviak, T. et al. *Dev. Cell* **35**, 366–382 (2015).
4. Rossant, J. & Tam, P. P. L. *Dev. Cell* **57**, 152–165 (2022).
5. Boroviak, T. et al. *Development* **145**, dev167833 (2018).
6. Bergmann, S. et al. *Nature* https://doi.org/10.1038/s41586-022-04953-1 (2022).
7. Cui, G. et al. *bioRxiv* https://doi.org/10.1101/2022.01.26.474719 (2022).
8. Shao, Y. et al. *Nat. Mater.* **16**, 419–425 (2017).
9. Zheng, Y. et al. *Nature* **573**, 421–425 (2019).
10. Boroviak, T. & Nichols, J. *Development* **144**, 175–186 (2017).

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Patrick P. L. Tam.